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A Phase I Dose-Escalation Trial of High-Dose Melphalan with Palifermin for Cytoprotection Followed by Autologous Stem Cell Transplantation for Patients with Multiple Myeloma with Normal Renal Function

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A B S T R A C T

Melphalan 200 mg/m^2 is the standard conditioning regimen for patients with multiple myeloma (MM) with normal renal function (NRF) undergoing autologous stem cell transplant (ASCT). In an effort to escalate the dose of melphalan and to improve the efficacy, we designed a dose-escalation study of melphalan in conjunction with palifermin in patients with NRF, with the hope that a higher dose of melphalan can be administered with an acceptable degree of oral mucositis (OM). We enrolled 19 patients (18 evaluable) with NRF. Dose-escalation of melphalan administered on day −2 began at 200 mg/m^2 with palifermin administered at a fixed dose of 60 mcg/kg/day. Palifermin was given as an i.v. bolus on day −5, −4, and −3, and then on day +1, +2, and +3. Subsequent dose escalations of melphalan were done at 20 mg/m^2 increments up to a maximum dose of 280 mg/m^2. Of 18 evaluable patients, there were no treatment-related deaths by day 100. The median age was 48.5 years (range, 33-65 years). The most common adverse events related to palifermin included rash (18 events, no ≥grade 3 events), elevation of amylase (10 events, 4 were grade 3 but asymptomatic), and lipase (5 events, 2 were grade 3 but asymptomatic), edema (11 events, no ≥grade 3). The overall incidence of OM grade 3 was 44% (8/18) with a median duration of severe mucositis of 5 days (range, 3-6 days). Eleven patients (61%) required opioid analgesics. None of the patients received total parenteral nutrition (TPN)/nasogastric feeding. Two of 6 patients who were given melphalan 280 mg/m^2 did not develop OM. Cardiac dose-limiting toxicity (DLT) in the form of atrial fibrillation did occur in 1 of 6 patients treated with melphalan 280 mg/m^2. Palifermin has permitted safe dose escalation of melphalan up to 280 mg/m^2, thus reaching the cumulative dosage of melphalan administered in tandem ASCT. This higher dose of melphalan has the potential to improve the efficacy and, hopefully, outcomes of patients with MM with a single ASCT. A phase 2 trial is necessary to better delineate the antimyeloma efficacy of this regimen.

INTRODUCTION

High-dose chemotherapy followed by autologous stem cell transplant (ASCT) has shown improved progression-free survival and reduced overall mortality compared to conventional chemotherapy in patients with multiple myeloma (MM) [1-5]. In patients with normal renal function (creatinine clearance ≥60 mL/min/1.73 m^2), melphalan administered at a dose of 200 mg/m^2 is considered the standard conditioning regimen [6,7]. Melphalan has a dose–response antimyeloma effect, and higher doses could potentially improve outcomes when used as a conditioning regimen for ASCT [8]. Attempts to improve response rates have been made by intensification of the conditioning regimen. Unfortunately, these attempts have encountered dose limiting toxicities (DLTs) such as severe oral and gastrointestinal mucositis [9-12]. Moreau et al. [9] showed that it is feasible to administer melphalan 220 mg/m^2, but significant oral mucositis (OM), delayed platelet engraftment, and cardiac arrhythmias were observed.

Attempts to minimize the incidence and severity of OM have included the use of cytoprotective agents including amifostine, which have allowed the dose of melphalan to be increased to 280 mg/m^2. Cardiac toxicity in the form of atrial fibrillation was seen in 3 of 36 patients treated with melphalan doses ≥280 mg/m^2 and was fatal in 1 patient given melphalan 300 mg/m^2 [13]. Amifostine has also been associated with infusional toxicities, including hypotension and nausea, and is currently not recommended for prevention of OM in the setting of hematologic malignancies [13-16]. Oral cryotherapy also reportedly reduces OM related to high dose melphalan. Lilleby et al. [17] used oral cryotherapy in patients undergoing ASCT with melphalan 200 mg/m^2. Although decreased incidence of OM was noticed in this group, dose escalation of melphalan was not attempted.

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Palifermin (Kepivance)® is a recombinant human keratinocyte growth factor approved for the prevention of OM in patients undergoing chemo/radiotherapy for hematological malignancies [18-21]. Keratinocyte growth factor was originally derived from the embryonic lung fibroblasts line and has a target-specific mitogenic action on the epithelial cells. Palifermin has been shown to decrease OM in patients taking melphalan as the conditioning regimen for their transplantation [22]. We have recently demonstrated that palifermin permitted safe dose escalation of melphalan up to 180 mg/m^2 in nondialysis-dependent myeloma patients with creatinine clearance ≤60 mL/min/1.73 M^2 [23]. The approximate cost of palifermin is $4700 for a 5-mg vial. Palifermin seems to be a costly option compared to oral cryotherapy, but its use could be justified if dose escalation of melphalan is achieved with acceptable toxicity and translates into improve disease response. Palifermin can lead to decreased toxicity related to melphalan, decreased hospital stays, decreased use of total parenteral nutrition (TPN), and narcotics, which further justifies its cost. We have designed this phase I dose escalation trial to determine the maximal tolerated dose (MTD) of melphalan when used with palifermin in patients with normal renal function who were undergoing ASCT for multiple myeloma (MM).

PATIENTS AND METHODS

This phase I trial was registered in the clinicaltrials.gov database (NCT00482846). The study was conducted at Barbara Ann Karmanos Cancer Institute, in Detroit, Michigan, approved by the Wayne State University Institutional Review Board, and conducted in accordance with the Declaration of Helsinki.

Study Design

Our primary objective was to determine the MTD of melphalan when treated with palifermin in order to prevent OM in patients with normal renal function who were undergoing ASCT for myeloma. Evaluation of the efficacy of this regimen, regimen-related toxicities, and the overall response to therapy at day +100 constituted the secondary objectives. This study used the Common Toxicity Criteria (CTC), version 3.0, for adverse event reporting [24].

This was a typical 3+3 phase I design. Dose level 1 began at the conventional transplantation dose of melphalan 200 mg/m^2 with palifermin. Subsequent melphalan dose escalations were done at 20 mg/m^2 increments in cohorts of 3 patients. Grade 4 OM, grade 4 diarrhea, and ≥grade 3 cardiac toxicity were considered DLT for melphalan; grade 3 or 4 hematological toxicity were considered expected due to ASCT. Grade 3 or above skin rash and grade 4 symptomatic elevations in amylase and lipase were considered DLT for palifermin. Improvement in incidence and severity of OM was the experimental objective of the study, and initially at the time of enrollment in level 1, grade 4 OM was not specified as DLT. Because of safety concerns, the protocol was later amended and grade 4 OM was considered a DLT. If no DLT events were noted within a cohort by day +30 after ASCT, the next cohort of 3 patients was enrolled at the next dose level. Dose escalations were to stop if ≥2 DLT events occurred at a single melphalan dose level, with that dose declared as the maximal administered dose and the previous dose level as the MTD. If a single DLT event was noted, 3 additional patients were entered at that dose level, and dose escalation proceeded only if no additional DLT events (ie, 1 of 6) were noted. If 1 or more of these 3 additional patients have DLT, then dose escalation was stopped, and this dose was to be declared the maximally administered dose and the previous dose level as the MTD. If a full cohort of 3 patients was entered at a given level without the observation of DLT, then dose escalation to the next level was permitted. Based on severe cardiac toxicities noted at melphalan ≥280 mg/m^2 seen by Spencer et al. [13], we allowed dose escalation only up to 280 mg/m^2. A patient failing to receive all 6 palifermin doses was declared ineligible and replaced on that dose level. Institution guidelines were followed for apheresis and a minimum of 2.0 × 10^6 CD34+ cells/kg were required to proceed to ASCT. The stem cell product was cryopreserved after apheresis and was reinfused according to standard practice. All study days are numbered with respect to the day of ASCT, which is defined as study day 0.

Eligibility

Patients were eligible if they qualified for ASCT per institutional criteria and had at least 2.0 × 10^6 CD34+ cells/kg cryopreserved. Other requirements included an Eastern Cooperative Oncology Group performance status of ≤2, MM stage 2/3, age ≥18 years, creatinine clearance >60 mL/min/1.73 m^2, total bilirubin <1.5 × institutional upper limit of normal, alanine aminotransferase and aspartate aminotransferase <3 × institutional upper limit of normal. Patients with baseline oral lesions, history of allergic reactions to melphalan, or prior exposure to palifermin were ineligible.

Dose calculations

The melphalan dose was calculated using the actual body weight (ABW) except when the ABW was >40% above the ideal body weight (IBW), in which case adjusted body weight (AdBW) was used: men: IBW (kg) = 50 + 0.91 × (height in cm − 152); women: IBW (kg) = 45 + 0.91 × (height in cm − 152) and AdBW (kg) = IBW + 0.25 × (ABW − IBW). The palifermin dose was 60 mcg/kg/day of ABW unless the patient's ABW was >40% above the IBW, and then the AdBW was used for the dose. Palifermin was administered on days −5,−4, and −3, and then repeated on day +1, +2, and +3 (peripheral blood stem cells were infused on day 0). There was a 24-hour interval between the palifermin and melphalan administration (day −2). Patients received palifermin as a once-daily i.v. bolus. No palifermin dose adjustments were allowed. Filgrastim was administered subcutaneously at a dose of 5 mcg/kg/day, starting on day +6 and continued until the absolute neutrophil count was >1500/mm^3 for 3 consecutive days.

Patient monitoring and follow-up

Patients who received all 6 doses of palifermin were followed until day +100. Disease response to treatment was assessed on day +28 and day +100(+/−7 days). Starting on day −2 with the administration of high-dose melphalan, oral cavity assessments were performed by the bone marrow transplant (BMT) attending daily using the World Health Organization (WHO) oral toxicity scale and continued until OM resolved completely (WHO = 0) or until day +28, whichever came later (Table 1). If a patient was discharged from the hospital without complete resolution of OM, that patient was then followed twice weekly in the outpatient clinic by the BMT attending until complete resolution.

Table 1
Oral Mucositis Assessment Scales

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
WHO	No changes	Soreness with erythema	Erythema, ulcers, can eat solids	Ulcers, liquid diet only	Alimentation not possible
NCI CTC (for BMT)	Not applicable	Painless ulcer or mild soreness without a lesion	Painful erythema, edema, or ulcers, but can swallow	Painful erythema, edema, or ulcers preventing swallowing or requiring hydrations or nutritional support	Severe ulcerations requiring prophylactic intubation or resulting in documented aspiration pneumonia
Bearman criteria	Not applicable	Pain and/or ulceration not requiring a continuous i.v. narcotic drug	Pain and/or ulceration requiring a continuous i.v. narcotic drug (morphine drip)	Severe ulceration and/or mucositis requiring preventative intubation, or resulting in documented aspiration pneumonia with or without intubation	Death

WHO indicates World Health Organization; NCI, National Cancer Institute; CTC, Common Toxicity Criteria; BMT, bone marrow transplant.

RESULTS

Patient Characteristics

Nineteen patients were enrolled between May 2007 and September 2009. One patient was removed due to the inability to receive all 6 doses of palifermin. This patient received melphalan 200 mg/m^2. The patient revoked his consent after 4 doses of palifermin because he developed grade 3 skin rash. No other grade 3 toxicity was observed while the patient was enrolled in the study. The patient did not develop any OM.

The baseline characteristics and previous treatment regimen of the 18 evaluable patients are summarized in Table 2 and Table 3, respectively. Eleven patients (61%) were men, and the median age of the whole group was 48.5 years (range, 33-65 years). The median creatinine clearance was 108 mL/min/1.73 m^2 (range, 61-240). All patients had a Karnofsky performance score $\geq$70%. The median number of CD34+ infused was 4.78 cells/kg $\times$ 10^6 (range, 2.18-11.36). Melphalan was given in doses of up to and including 280 mg/m^2 (n = 6). All 18 patients were evaluable for response at 100 days posttransplantation. The median number of days for neutrophil engraftment was 12 (range, 10-13 days). The median number of days to platelet engraftment was 19.5 (range, 0-29 days). The median duration of hospitalization was 15.5 days (range, 14-22 days).

Mucositis Occurrences

The overall incidence of, and OM $\geq$grade 3 was 44% (8 of 18 patients) the median time to resolution of any OM was 10 days (range, 4-20 days) (Table 4). The median duration of severe OM was 5 days (range, 3-6 days). Grade 4 OM was seen in only 1 patient at level 1 (melphalan 200 mg/m^2), lasting 3 days. Accrual was allowed to the next level as grade 4 OM was not defined as DLT at the time of accrual in level 1, which was later amended. Five of 18 patients developed no OM. None of the patients needed TPN including the level 1 patient with grade 4 OM. Only 1 of 6 patients enrolled in level 5 (melphalan 280 mg/m^2) suffered from grade 3 OM.

Table 2
Patient Characteristics

Sex: male (%)	11 (61)
Median age (range)	48.5 (33-65)
Race: white	15 (83)
Median creatinine clearance (range)	108 (61-240)
Durie-Salmon stage: no. (%)	
Stage 2	7 (39)
Stage 3	11 (61)
Isotypes: No. (%)	
IgG kappa	7 (39)
IgG lambda	2 (11)
IgA kappa	5 (28)
IgA lambda	1 (6)
Kappa light chain	1 (6)
Lambda light chain	1 (6)
Nonsecretory	1 (6)
Previous radiation	4 (22)
Karnofsky performance scale: no. (%)	
70	2 (11)
80	7 (39)
90	9 (50)
Disease status at the time of transplantation: No. (%)	
VGPR	6 (33)
PD	3 (17)
CR	2 (11)
PR	6 (33)
SD	1 (6)
Median duration of hospital stay (range)	15.5 (14-22)

VGPR indicates very good partial response; PD, progressive disease; CR, complete remission; PR, partial remission; SD, stable disease.

Table 3
Previous Treatment Regimen

Dose Level	Disease Status at Transplantation	Pre-BMT Treatment Regimens (Number of Cycles When Known)
1	PR	Kyphoplasty, radiation, pulse dexamethasone (4), lenalidomide/dexamethasone/pamidronate
1	PD	Melphalan/prednisone (5), thalidomide/dexamethasone
1	PD	Local radiation and spinal fusion, thalidomide/dexamethasone (4)
2	PR	Dexamethasone/zoledronic acid (3), lenalidomide/dexamethasone
2	PD	Radiation, laminectomy, lenalidomide/dexamethasone/darbepoetin alpha
2	VGPR	Vincristine/adriamycin/dexamethasone (4), melphalan 200 mg/m^2 with auto-PBSCT, pamidronate, thalidomide/dexamethasone, bortezomib (4), lenalidomide
3	VGPR	Lenalidomide/dexamethasone (4), bortezomib/dexamethasone (2)
3	CR	Kyphoplasty, radiation, lenalidomide/dexamethasone/zoledronic acid (6)
3	PR	Adriamycin/bortezomib/dexamethasone/zoledronic acid (4), lenalidomide/dexamethasone (4)
4	PR	Kyphoplasty, DVD (1), lenalidomide/dexamethasone, bortezomib/dexamethasone (3)
4	PR	DVD (4)
4	PR	DVD (6), lenalidomide/dexamethasone/zoledronic acid (3)
5	VGPR	Radiation, thalidomide/dexamethasone/zoledronic acid (4)
5	CR	Radiation, bortezomib/dexamethasone (4)
5	VGPR	Bortezomib/lenalidomide/dexamethasone/pamidronate (4)
5	VGPR	Bortezomib/dexamethasone (1), bortezomib/lenalidomide/dexamethasone (3)
5	VGPR	Radiation, lenalidomide/dexamethasone/zoledronic acid (4)
5	SD	Surgery, DVD (3), lenalidomide/bortezomib/dexamethasone (4)

BMT indicates bone marrow transplant; PR, partial remission; PD, progressive disease; VGPR, very good partial response; PBSCT, peripheral blood stem cell transplantation; CR, complete remission; DVD, doxil/vincristine/dexamethasone.

Adverse Events

The patients were monitored for side effects related to melphalan and palifermin (Table 5). The most common adverse events related to palifermin included rash (18 events, no $\geq$grade 3 events), elevation of amylase (10 events, 4 were grade 3 asymptomatic), lipase (5 events, 2 were grade 3 asymptomatic), and edema (11 events, no $\geq$grade 3 events). Cardiac toxicity (DLT) in the form of atrial fibrillation, which could be related to melphalan, occurred in 1 of 6 patients treated with melphalan 280 mg/m^2. Three more patients were added to that dose level with no recurrences of that toxicity. Eleven patients (61%) required opioid analgesics; none needed TPN/nasogastric feeding. Other adverse events related to the treatment were vomiting, which was reported in 15 patients, and diarrhea was observed in 13 patients. Grade 3 diarrhea was seen in 2 patients. Five of the 13

Table 4
Melphalan Dose and Severity of OM

Patients	WHO-OM Score Range	Duration of Severe OM (Grade 3)*	Days to Resolution of OM
Level 1 = melphalan 200			
1*	2-4	5	9
2	1-2	-	8
3	1-3	6	10
Level 2 = melphalan 220			
4	0	-	-
5	1-3	5	10
6	2-3	6	11
Level 3 = melphalan 240			
7	0	-	-
8	1-3	5	12
9	1-2	-	12
Level 4 = melphalan 260			
10	0	-	-
11	1-3	6	20
12	2-3	5	16
Level 5 = melphalan 280			
13	0	-	-
14	0-1	-	4
15	0-1	-	8
16	1-2	-	10
17	1-3	3	17
18	0	-	-

OM indicates oral mucositis; WHO, World Health Organization.
* Only 1 patient in the whole group receiving melphalan 200 mg/m^2 developed grade 4 OM for 3 days.

patients with diarrhea had *Clostridium difficile* infection. Five of 13 patients had positive blood cultures. No infection-related death was noted. The highest allowable level 5 in our study received melphalan 280 mg/m^2. Further dose escalation was not allowed because of cardiac toxicity reported at melphalan 300 mg/m^2 in earlier studies [13]. Hence, we did not reach the maximal administered dose.

Response

The responses to treatment are shown in Table 6. Complete response was seen in 3 patients. Two patients were given maintenance treatment within the 100-day follow-up period. No deaths were observed at 100 days post-transplantation. There was no treatment-related death. Tumor responses have been noted at all melphalan doses.

Table 5
Adverse Events

	Grade 1	Grade 2	Grade 3	Grade 4
Palifermin-Related Adverse Effects: No. of Patients (%)				
Skin rash	7 (39)	11 (61)	0	0
Elevated amylase	5 (28)	1 (6)	4 (22)	0
Elevated lipase	3 (17)	2 (11)	0	0
White coating of the tongue*	15 (83)			
Edema*	11 (61)			
Melphalan and ASCT-Related Adverse Effects: No. of Patients				
Diarrhea	5 (28)	6 (33) (3 had C. diff)	2 (11) (2 had C. diff)	0
Vomiting	12 (67)	3 (17)	0	0
Cardiac toxicity	0	0	1 (6) (atrial flutter)	0
Positive blood cultures*	5 (28)			

ASCT indicates autologous stem cell transplant; C. diff, *Clostridium difficile*.
* Not graded.

Table 6
Disease Response

Dose Level #	Dose of Melphalan	Disease Status at Transplantation	Disease Status at Day 100
1	200	PR	CR
1	200	PD	PR
1	200	PD	SD
2	220	PR	PR
2	220	PD	SD
2	220	VGPR	SD
3	240	VGPR	VGPR
3	240	CR	CR
3	240	PR	PR
4	260	PR	PR
4	260	PR	VGPR
4	260	PR	SD
5	280	VGPR	SD
5	280	CR	CR
5	280	VGPR	SD
5	280	VGPR	PR
5	280	VGPR	SD
5	280	SD	VGPR

PR indicates partial remission; CR, complete remission; PD, progressive disease; SD, stable disease; VGPR, very good partial response.

DISCUSSION

The curative treatment of MM remains elusive. Although high-dose chemotherapy followed by ASCT has shown improved survival rates, relapse continues to limit long-term survival. Mucosal barrier injury (MBI) is a major cause of morbidity and mortality in patients with MM undergoing ASCT with melphalan as a conditioning regimen [25,26]. Effective muco-protection could be a way to intensify the dose of melphalan, as was seen in our study. We were able to escalate the melphalan safely up to 280 mg/m^2 in patients with normal renal function by addition of palifermin. Our study results are in accordance with the retrospective study by Kobbe et al. [22] who showed improved incidence of OM when using a 3-day course of palifermin before ASCT with melphalan 200 mg/m^2. Earlier, we demonstrated that the melphalan dose could be safely increased up to 180 mg/m^2 in patients with chronic kidney disease. Incidence of severe OM observed in our study was better as compared to other studies reported in patients with chronic kidney disease [23].

The incidence of $\geq$grade 3 OM was 44% in our study. Moreau et al. [7] demonstrated an incidence of severe OM (grade $>$3) as 42% in newly diagnosed patients with MM conditioned with melphalan 200 mg/m^2. Another study using melphalan 220 mg/m^2 showed an incidence of grade 4 mucositis as 63% [9]. We consider the incidence of grade 3 or above OM in our group of previously treated patients acceptable, as the median duration of severe OM was only 5 days (range, 3-6 days) and the patients were able to have liquid diets (WHO grade 3). Therefore, none of the patients in our study needed TPN. The need for TPN use was determined by the rounding physician based on multiple factors, including but not limited to incidence/severity of diarrhea, nausea, vomiting, functional capacity, and electrolyte disturbances. Eleven patients needed narcotics for pain relief, but they were not considered candidates for TPN based on the above-mentioned factors.

DLT in the form of atrial fibrillation was noted in a patient receiving a melphalan dose of 280 mg/m^2. Further dose escalation was stopped and the next 3 patients were enrolled at the same dose level. In the 3 additional patients, no DLTs were seen and 280 mg/m^2 was declared the MTD. Dose

escalation beyond 280 mg/m^2 was not allowed in our trial because melphalan 300 mg/m^2 had shown cardiotoxicity and related mortality in earlier trials [13]. *Clostridium difficile* toxin was isolated from stool in 5 of 18 patients. Five patients had positive blood cultures in our study. There was no infection-related death. MBI can lead to an increased rate of neutropenic infections and treatment-related mortality [27,28]. Cytoprotective action of palifermin on MBI could have a potential role in decreasing the rate of invasive infection. Palifermin through its preventive role as a muco-protective agent can lead to lower rates of infection and better nutritional intake, which could lead to improved overall outcome for patients with myeloma who are undergoing ASCT and justify the cost of palifermin. The usefulness of this agent could be further enhanced by combining it with cryotherapy, which by itself has shown to improve OM [17]. Lilleby et al. [17] had demonstrated muco-protective action of oral cryotherapy in patients with MM undergoing ASCT with melphalan 200 mg/m^2. Their study was not designed for dose escalation. TPN, when needed, was administered for a median of 2 days (range, 0-15 days). They used the National Cancer Institute (NCI) CTC criteria for OM assessment [17].

It does seem that there is a remarkable grading difference in OM assessment scales, making comparison of protective benefit across trials difficult (Table 1). As mentioned above, Lilleby et al. [17] used NCI CTC criteria for OM assessment. According to NCI criteria, TPN use will result in grading of OM as grade 3, whereas according to the WHO scale (Table 1), TPN use will likely categorize the patient as grade 4 OM. Similarly, Spencer et al. [13] had used Seattle (Bearman) criteria to assess OM in their dose escalation trial with amifostine, in which grade 4 toxicity was death. We decided to use the WHO scale because this scale seems to combine both objective findings by examination (ulceration and redness) and functional capacity such as inability to eat solid food or no food at all.

Moreover, this scale was the primary scale used in the pivotal trial by Spielberger et al. [21], which led to approval of palifermin for the prevention of OM in patients undergoing chemo/radiotherapy for hematological malignancies.

Palifermin seems to be well tolerated in multiple studies. The common side effects, which have been previously noted with palifermin, were also encountered in our study. These included a white coating of the tongue, rash, edema, and elevated amylase and lipase [19-21]. Meropol et al. [20] reported elevated amylase in 48 of 54 patients and lipase in 50 of 54 patients treated with varying doses of palifermin. Higher elevations were noted at higher doses. In the study by Spielberger et al. [21], common side effects reported by palifermin recipients were rash (55%), pruritus (50%), erythema (47%), cough (34%), and edema (29%). Asymptomatic increase in amylase and lipase was also noted. These side effects are manifestations of its physiological action of stimulating the growth of epithelial cells [29]. There was no DLT secondary to palifermin use in our study. Our study suggests that palifermin given at a dose of 60 mcg/kg/day for 3 days before conditioning and 3 days after the ASCT allowed a melphalan dose escalation to 280 mg/m^2 in patients with MM with normal renal function. Augmented cell killing may be achieved with doses of melphalan above what has been given historically without palifermin, thus breaking the present-day barriers of DLTs in ASCT. Our trial was a dose-finding trial and the primary objective was to determine the MTD of melphalan when used in conjunction with palifermin in patients with normal renal function (NRF) who are undergoing ASCT for MM. A phase 2 trial is necessary to better delineate the antimyeloma efficacy of this combination in terms of safety profile and clinical responses. We recommend using palifermin with melphalan 280 mg/m^2, which was the MTD determined by our trial. Modification of palifermin dosing could also be tried with or without combining it with other agents.

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